6th Toyama-Basel Joint Symposium 2021 –Program

Online by Zoom **Login details after the program**

15th September

09:00 / 16:00 (Basel/JST) Opening of Symposium
Prof. Matthias Hamburger (Basel) and
Dir. Prof. Kiyoshi Takatsu (Toyama)

Session 1

09:15 / 16:15 Prof. Scott McNeil (University of Basel)
Nanomedicine: the Toolkit for Drug Delivery

09:55 / 16:55 Prof. Stephan Krähenbühl (University of Basel)
Preclinical Development of a Small Molecular Weight Integrin Inhibitor

10:35 / 17:35 Prof. Yoshihiro Hayakawa (University of Toyama)
Understanding Host Defence System and its Application to Drug Discovery

11:15 / 18:15 Prof. Yoshimi Nakagawa (University of Toyama)
Therapeutic Strategy for Hyperlipidemia by Transcriptional Regulation of Systemic Lipid Metabolism in Intestine-Liver Association

Chairs: Prof. Tatsuya Murakami (Toyama) and Prof. Jörg Huwyler (Basel)

12:55 / 18:55 End of Day 1

16th September

09:00 / 16:00 (Basel/JST)

Session 2

09:00 / 16:00 Prof. Yasuhito Koyama (Toyama Prefectural University)
Impact of Glycon on Self-Assembly Behaviors of Bioactive Glycosides

09:40 / 16:40 Assistant Prof. Aki Kohyama (University of Toyama)
Synthesis of Guggulsterone Analogues and Their Biological Activities

10:20 / 17:20 Prof. Markus Lill (University of Basel)
Deep learning for structure-based drug design

11:00 / 18:00	Prof. Daniel Ricklin (University of Basel) **Therapeutic Modulation of Adverse Host Defense Reactions: A Treasure Chest for Academic Drug Discovery** Chairs: Dir. Kiyoshi Takatsu (Toyama) and Prof. Olivier Potterat (Basel)
11:40 / 18:40	End of Day 2

17th September
09:00 / 16:00 (Basel/JST)

Session 3

09:00 / 16:00	Prof. Henriette Meyer zu Schwabedissen (University of Basel) **Organic Anion Transporting Polypeptides – the Good or the Bad in Drug Metabolism?**
09:40 / 16:40	Prof. Olivier Potterat (University of Basel) **Library-based Discovery of Bioactive Natural Products**
10:20 / 17:20	Associate Prof. Yukihiro Furusawa (Toyama Prefectural University) **Commensal Microbiota maintains Gut Homeostasis through its Metabolic Products and Epigenetic Modifications**
11:00 / 18:00	Chief Investigator Yasuharu Watanabe (Toyama Prefectural Institute for Pharmaceutical Research) **Crosstalk between Neutrophils and Adipocytes exacerbates Adipose Tissue Inflammation in the Progression of Type 2 Diabetes** Chairs: Prof. Markus Lill (Basel) and Prof. Hideki Sakai (Toyama)
11:40 / 18:40	**Winners of the poster awards: Ceremony and poster prizes**
12:00 / 19:00	Closing Remarks Dir. Kiyoshi Takatsu (Toyama) and Prof. Matthias Hamburger (Basel)
12:15 / 19:15	End of Symposium

Speakers

and

abstracts of presentations

Prof. Dr. Scott McNeil

Dept. of Pharmaceutical Sciences, University of Basel.

Nanomedicine: the toolkit for drug delivery

Abstract

Nanomedicines are now widely approved for human use, against diseases such as cancer, infectious disease, and conditions such as anemia. Compared to a drug's "legacy" formulation, a nanomedicine-based formulation of the drug offer improved pharmacokinetics and safety profiles. For instance, a pharmaceutical company may screen several hundred-thousand small molecules against a target of interest. Very few of these molecules will be compatible with futher development (i.e., Lipinski's rule-of-five), due to their inherent hydrophobicity. Nanomedicine offers the drug developer a 'tool kit' to overcome these limitations, since solubility becomes a function of the nano-carrier instead of the molecule itself. This presentation will discuss the current state of the nanomedicine field and its future outlook. It will also discuss methods for characterising nanoformulations, and the nanomedicines' interaction with the immune system.

Short CV

Prof. Dr. Scott McNeil is the Head of the Nanopharmaceutical and Regulatory Science Group within the Department of Pharmaceutical Sciences at the University of Basel. He received his B.S. degree in Chemistry from Portland State University and his Ph.D. in Cell Biology and Anatomy from Oregon Health Sciences University. Scientists within his group develop and characterize novel nano-based formulations, with the goal of improving the therapeutic index of active pharmaceutical ingredients. Prof. McNeil’s research involves using nanomedicines to deliver enzymes for the treatment of lysosomal storage diseases. In collaboration with other research institutions, he also identifies and investigates the critical quality attributes (CQAs) of nanopharmaceuticals and nanosimilars, such as mechanisms of action, safety, and practical application issues. Prior to joining the University of Basel in 2020, he was the Director of the Nanotechnology Characterization Laboratory (NCL) at the National Cancer Institute. In addition to his academic career, McNeil served for twenty years in the US Army.

Prof. Dr. Stephan Krähenbühl

Clinical Pharmacology & Toxicology
Department of Pharmaceutical Sciences, University of Basel, Switzerland

LFA-1: Preclinical development of a small molecular weight integrin inhibitor

Stephan Krähenbühl was born on November 29, 1953, near Berne in Switzerland. He graduated from the School of Pharmacy of the University of Berne in 1978 and got his Ph.D. in Pharmacy in 1981 in Berne. In 1985, he graduated from the School of Medicine of the University of Berne, where he got his M.D. the same year. From 1985 to 1999 he obtained a formation in internal medicine, hepatology, clinical pharmacology and clinical chemistry at the University Hospitals of Berne and Zurich in Switzerland and at the Case Western Reserve University in Cleveland, OH, USA. Since the year 2000, he is chief physician and head of the Division of Clinical Pharmacology & Toxicology at the University Hospital of Basel. At he same time, he is one of the chief physicians in internal medicine at the University Hospital of Basel. He gives lectures in clinical pharmacology, toxicology and clinical nutrition for students in medicine and pharmacy at the University of Basel and at the Swiss Federal Institute of Technology in Zurich. His scientific interests are drug metabolism and toxicity, energy metabolism (in particular mitochondrial function), drug-drug interactions and drug administration in patients with impaired organ function. He has published more than two hundred scientific articles in these areas. He is currently heading the medical experts committee of the Swiss Drug Administration

Professor, Yoshihiro Hayakawa

Section of Host Defences, Institute of Natural Medicine, University of Toyama

Understanding host defence system and its application to drug discovery

The host defence system is a multifaceted immune system of unique, yet highly integrated, responses to potentially harmful antigens, infections or mutated cells, such as cancer cells. The immune system is composed of an innate and an adaptive response, and innate immunity is constitutively present and is mobilized immediately following invasion of non-self-antigens. In this context, our Lab studies the control of immunological diseases focusing on innate immune cells, particularly the biology of natural killer (NK) cells and their importance in the control of cancer progression and metastasis. In clinic, an inverse correlation between the levels of circulating or tumor-infiltrating NK cells and the metastatic spread in several types of cancer patients has been reported. Anti-tumor activity of NK cell is mainly induced by the activation receptors, whereas the counter negative signal by recognizing self MHC molecules or other self-related molecules dampens such activation signal. NK cells control tumor metastasis through its granule-mediated or death ligand-induced cytotoxicity, along with the production of anti-tumor cytokine IFN-g. While the subsets of NK cell display diversities in their function and tissue distribution, there is no clear evidence whether circulating/infiltrating NK cells and/or tissue-resident NK cells play a dominant role in controlling tumor growth and metastasis. In this presentation, I would like to share the current understanding and our recent efforts on how NK cells control tumor growth, progression and distant metastasis.

Education and professional back ground:

2001	Ph.D., Faculty of Pharmaceutical Science, Toyama Medical and Pharmaceutical University
2001–2006	Senior Research Officer, Cancer Immunology Program, Peter MacCallum Cancer Centre, Melbourne, Australia
2007–2009	Group Leader (Research Fellow), Biomarker Group, Pharmacology Department, Tsukuba Research Institute, Merck Research Laboratories
2009–2012	Associate Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo
2017–	Professor, Institute of Natural Medicine, University of Toyama, Japan
2021–	Director, Institute of Natural Medicine, University of Toyama,

Awards:

2013: Young Investigator's Award, Japanese Cancer Association
2012: Young Investigator's Award, Japanese Association of Metastasis Research
2003: Cancer Research Institute, Postdoctoral Training Fellowship
2002: Uehara Memorial Foundation, Research Fellowship

References:

1) Fujiwara T, Hayakawa Y *et al*. (2021) ***J Immunol Methods*** 491: 112993; **2)** Fujimoto M, Hayakawa Y *et al*. (2021) ***Cancer Sci*** 112(4): 1633-1643; **3)** Miyazato K, Hayakawa Y *et al.* (2020) ***Cancer Sci*** 111(8): 2770-2778; **4)** Miyazato K & Hayakawa Y (2020) ***Cancer Sci*** 111(6): 1869-1875; **5)** Yamamoto Y, Hayakawa Y *et al*. (2018) ***Cancer Sci*** 109(9): 2670-2676; **6)** Ogura K, Hayakawa Y. *et al*. (2018) ***Cancer Immunol Res*** 6(3): 348-357.

Professor Yoshimi Nakagawa, PhD.

Division of Complex Biosystem Research,

Institute of Natural Medicine, University of Toyama

Therapeutic Strategy for Hyperlipidemia by Transcriptional Regulation of Systemic Lipid Metabolism in Intestine-Liver Association

Abstract

CREBH is a membrane-bound transcription factor, which expressed in only the liver and small intestine. CREBH is activated during starvation and controls the onset of gene expression of the improvement of carbohydrate and lipid metabolism in the liver. We clarified that CREBH could contribute to the therapeutic strategy of lifestyle-related diseases. CREBH-deficient mice developed high-fat diet-induced abnormal fatty liver, hepatitis, and small intestine structural abnormalities, and then exacerbated these diseases due to abnormal nutrition metabolism. Furthermore, we clarified that CREBH deficiency induces atherosclerosis and liver cancer, which are terminal states of lifestyle-related diseases. Furthermore, we newly generated tissue-specific CREBH overexpression/deficiency mice by creating genetically modified mice with the CRISPR/Cas9 system. Non-alcoholic fatty liver and arteriosclerosis were aggravated in even the liver- or small intestine-specific KO mice. Liver-specific CREBH Tg mice exhibit severe growth delay by inhibiting growth hormone signaling in the liver. CREBH has a pivotal role in connecting starvation and growth delay. In this study, we clarified that CREBH plays a crucial role in the regulation of nutrient metabolism and nutrient absorption in the liver and small intestine, respectively, and is greatly involved in lifestyle-related diseases.

Short CV

2020 ~ Professor, Institute of Natural Medicine, University of Toyama
2014 ~ Associate Professor, International Institute for Integrative Sleep Medicine (IIIS), University of Tsukuba
2011 ~ Assistant Professor, Faculty of Medicine, University of Tsukuba
2010 ~ Postdoctoral Fellow, San Francisco General Hospital, University of California, San Francisco
2002 ~ Assistant Professor, Faculty of Medicine, University of Tsukuba

1. Nakagawa Y, et al. Starvation-induced transcription factor CREBH negatively governs body growth by controlling GH signaling. ***FASEB Journal*** 2021;35(6):e21663.
2. Nakagawa Y, et al. Enterohepatic Transcription Factor CREB3L3 Protects Atherosclerosis via SREBP Competitive Inhibition. ***Cell Mol Gastroenterol Hepatol.*** 2021;11(4):949-971.
3. Satoh A, Nakagawa Y, et al. CREBH improves diet-induced obesity, insulin resistance, and metabolic disturbances by FGF21-dependent and -independent mechanisms. ***iScience*** 2020;23(3):100930.

Professor, Yasuhito Koyama

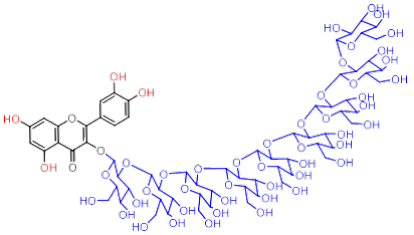
Department of Pharmaceutical Engineering,

Faculty of Engineering, Toyama Prefectural University

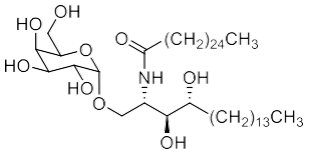
Impact of Glycon on Self-Assembly Behaviors of Bioactive Glycosides

Molecular self-assembly in water is one of the most prominent research areas in chemical and biological sciences. The associates in water have a potential usefulness as the nanocarrier of guest molecules. To modulate the morphology and properties of the associatesin water, scientists have considerably devoted their efforts on the skeletal design of amphiphilic molecules. On the other hand, we focus our attention on the use of amphiphiic glycosides as the component of associates. Amphiphilic glycosides are naturally abundant compounds, which are expected to form self-associates in water. However, the self-assembly behaviors of natural glycosides and their derivatives have not been systematically investigated in spite of its great importance. The evaluation of morphologies and properties of the associates should open new insights into glycoside chemistry such as the application of glycosides to nanocarriers and the elucidation of detailed pharmacological mechanism of bioactive glycosides.

Herein, we will show the synthesis and self-assembly behaviors of bioactive glycosides such as quercetin-3-*O*-glycosides[1-3] and α-galactosyl ceramide.[4] We will present the special effects of glycon on the self-assembly and thermal transition behaviors, which will be discussed through the comparison with those of the corresponding aglycons.



Bolaamphiphilic
Quercetin Polyglycoside (QP)



α-Galactosyl ceramide
(**GalCer**)

References:

1) Nargis, M.; Ihsan, A. B.; **Koyama, Y.*** *Langmuir*, **2020**, *36*, 10764.
2) Nargis, M.; Ihsan, A. B.; **Koyama, Y.*** *Chem. Lett.* **2020**, *49*, 896.
3) Nargis, M.; Ihsan, A. B.; **Koyama, Y.*** *RSC Adv.* **2019**, *9*, 33674.
4) Miyazaki, R. Nargis, M.; Ihsan, A. B.; Nakajima, N.; Hamada, M.; **Koyama, Y.*** *Langmuir*, **2021**, *37*, 7936.

Education:

1966-2001 B. Ms. Hokkaido University, Sapporo, Japan
2002-2004 Dr. Tohoku University, Sendai, Japan

Professional Career:

2005-2006 JSPS Postdoctral Research Fellow
2007-2012 Assistant Professor, Tokyo Institute of Technology, Tokyo, Japan
2013-2016 Associate Professor, Hokkaido University, Sapporo, Japan
2017-2020 Associate Professor, Toyama Prefectural University, Imizu, Japan
2021-present Professor, Toyama Prefectural University, Imizu, Japan

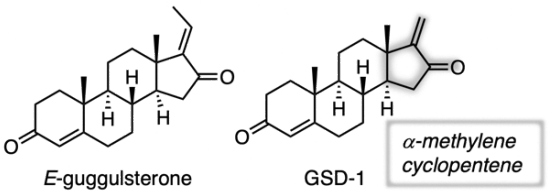
Assistant Professor, Aki Kohyama, Ph.D.

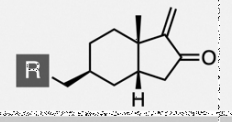
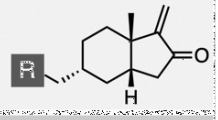
Faculty of Pharmaceutical Sciences, University of Toyama,
Toyama 930-0194, Japan

Synthesis of Guggulsterone Analogues and the NF-kB Inhibitory Activity

Abstract

Guggulsterone (GS), a phytochemical found in guggul (used in Indian traditional medicine), has various biological activities. In our laboratory, we have conducted structure-activity relationship (SAR) studies inspired by guggulsterone. In this presentation, we introduce a project to discover a NF-kB inhibitor from synthetic guggulsterone analogues (GSDs). In the first screening, we discovered that GSD-1 inhibited the activation of NF-kB moderately. GSD-1 contains α-methylene cyclopentenone, a highly reactive Michael acceptor. Therefore, a series of α-methylene cyclopentenonecompounds (MCPs) were designed, synthesized, and evaluated for their NF-kB inhibitory activities. Among ten MCPs, MCP-4b, 5b, 6b were active compounds, while the diastereomers (MCP-4a, 5a, 6a) were inactive. This result suggests the possibility that the modification of α-methylene cyclopentenone, a Michael acceptor as one of thePAINS (Pan-Assay Interference Compounds), regulates biological activity.



R		
Ph	MCP-4a	MCP-4b
OMe	MCP-5a	MCP-5b
CN	MCP-6a	MCP-5b

Short CV

B.Sc. (2011), **M.S.** (2013), **Ph.D.** (2016, Pharmaceutical Sciences),
Pharmaceutical Sciences, Tohoku University (Prof. Yoshiharu Iwabuchi)
Title of Ph.D. Thesis: Medicinal Chemistry Research about Cytotoxic C5-Curcuminoid Synthetic Study of Fusarisetin A for Development of Translocation Inhibitor
Assistant Professor (2016-present), Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Japan (Prof. Yuji Matsuya)

Selected Publication

Facile o-Quinodimethane Formation from Benzocyclobutenes Triggered by Staudinger Reaction at Ambient Temperature. Kohyama, A.; Koresawa, E.; Tsuge, K.; Matsuya, Y. *Chem. Commun*. **2019**, *55*, 6205-6208.

Synthesis of guggulsterone derivatives as potential anti-austerity agents against PANC-1 human pancreatic cancer cells. Kohyama, A.; Yokoyama, R.; Dibwe, D. F.; El-Mekkawy, S.; Meselhy, M. R.; Awale, S.; Matsuya, Y.
Bioorg. Med. Chem. Lett. **2020**, *30*, 126964.

Reversibility of thia-Michael reaction of the cytotoxic C5-curcuminoid and structure-activity relationship of the bis-thiol-adducts thereof. Kohyama, A.; Iwabuchi, Y. *et al*.
Org. Biomol. Chem. **2016**, *14,* 10683-10687.

An enantiocontrolled entry to the tricyclic polar segment of (+)-fusarisetin A. Kohyama, A.; Kanoh, N.; Kwon, E.; Iwabuchi, Y. *Tetrahedron Lett*. **2016**, *57,* 517-519.

Prof. Dr. Markus A. Lill

Computational Pharmacy,

Dept. of Pharmaceutical Sciences, University of Basel

Deep learning for structure-based drug design

Artificial intelligence methods based on deep neural networks play an increasingly integral part in all science areas ranging from physics, chemistry, biology, engineering, medicine to pharmaceutical research, as recently highlighted by the development of AlphaFold2 that largely solved the decades-long problem of protein structure prediction based on sequence. This development alone will have significant influence on rational structure-based drug discovery.

In this presentation, I will use selected examples from our own lab to highlight how deep neural networks are changing our approach towards computational drug discovery. Those developments range from de novo drug design, prediction of protein-ligand complex structures, the prediction of solvation effects as driving force for drug-target association and the modeling of dynamic aspects of protein-ligand interactions. I will also highlight that machine learning methods can no longer be considered as a black box, but provide deep insight into the underlying processes of protein-ligand binding and facilitate the identification of novel physicochemical aspects relevant to drug discovery. In this context, I will discuss our exploration of the different facets of (de)solvation upon ligand binding, in particular the recognition of the formation of enthalpically favorable networks of first-shell water molecules around solvent-exposed ligand moieties being an essential element for protein-ligand binding. Despite being currently neglected in drug discovery this hydration phenomenon could lead to new avenues in optimizing the free energy of ligand binding.

Markus A. Lill received his Diploma in Physics from the University of Erlangen-Nürnberg and in 2002 his Ph.D. from the Max Planck Institute for Biophysics, Frankfurt, Germany. He completed four years of Postdoctoral training at the Biographics Laboratory 3R and his Habilitation in 2006 at the University of Basel, Switzerland. He then became an Assistant Professor and 2012 Associate Professor for Computational Drug Design at Purdue University, USA. Currently, he is Professor for Computational Pharmacy at the University of Basel where his research is focused on the development and application of computational methods for drug discovery with a deep focus on physics-based artificial intelligence.

Prof. Dr. Daniel Ricklin

Molecular Pharmacy Group, Department of Pharmaceutical Sciences, University of Basel, Switzerland

Therapeutic Modulation of Adverse Host Defense Reactions: A Treasure Chest for Academic Drug Discovery

Although host defense pathways, including the complement, coagulation and contact systems, are designed to confer broad and instant protection from endo- and exogenous threats (*e.g.,* tissue damage, cell debris or microbial intruders), they may turn against the host when erroneously triggered and contribute to numerous clinical conditions. Organ transplantation serves as prominent example, in which the recognition of donor antigens and ischemia-induced damage signatures on endothelial cells may lead to thromboinflammatory complications and rejection. The need and potential for therapeutically interfering in adverse host defense pathway activation has been recognized by pharmaceutical industry, with several drug candidates reaching the clinic, but also offers an ideal playground for academic drug discovery. The presence of extracellular targets with high potential druggability (*e.g.,* serine proteases, GPCR's), the cascade organization of most pathway and the availability of physiological regulators and microbial evasion molecules that serve as templates or inspiration provide ample opportunities to develop innovative therapeutic concepts. With a focus on the complement system and ischemia-reperfusion injury (e.g., during transplantation, stroke or infarction), our group develops and evaluates therapeutics entities that interfere at various initiation, propagation and effector steps. Examples that are briefly introduced during the talk include parasite-derived and glycomimetic initiation inhibitors, protective coatings for biomaterials that recruit host regulators and peptide-based clinical candidates that broadly inhibit the activation and amplification of complement responses.

Daniel Ricklin studied Pharmaceutical Sciences at ETH Zurich and, after an internship in clinical proteomics, conducted a Ph.D. thesis in the group of Prof. Beat Ernst at the University of Basel, which sparked his interest in drug design and immune-modulatory therapies. In 2006, he joined the group of Prof. John Lambris at the University of Pennsylvania (USA) as a postdoctoral researcher with an initial focus on elucidating molecular aspects of the complement system in health and disease. Upon his appointment as Assistant/Associate Professor at the Perelman School of Medicine (University of Pennsylvania), his research focus shifted to therapeutic approaches of treating complement disorders. In 2016, he was offered a professorship at the Department of Pharmaceutical Sciences of the University of Basel and serves as head of the Molecular Pharmacy group since 2017. The emphasis of Daniel Ricklin's current research is on the therapeutic modulation of host defense pathways, including the complement and coagulation systems. Taking inspiration from microbial immune evasion strategies, and utilizing techniques such as peptide synthesis, protein engineering and medicinal chemistry, he aims to design novel therapeutic concepts with potential use in a broad range of clinical conditions, including immune, inflammatory, and biomaterial/transplant-induced disorders. The development portfolio ranges from leech-derived and glycomimetic inhibitors of complement initiation, protective surface coatings to prevent complement attack of transplants/materials and complement receptor modulators to next-generation analogs of the clinical complement inhibitor compstatin. As professor at the University of Basel, he is not only engaged in research and administrative activities but also teaches several courses on drug sciences and supervises bachelor, master and PhD students and postdoctoral researchers.

Prof. Dr. Henriette Meyer zu Schwabedissen

University of Basel, Department of Pharmaceutical Sciences, Biopharmacy

Organic Anion Transporting Polypeptides – the good or the bad in drug metabolism?

Drug Transporters are membrane proteins facilitating transmembrane transport. One family of drug transporters are the Organic Anion Transporting Polypeptides, which mediate cellular uptake of a variety of endogenous and exogenous molecules. Especially for the hepatic OATP1B-transporters, namely OATP1B1 and OATP1B3, it is known that their function and activity is of clinical relevance. Indeed, changes in activity occur due to genetic variability and/or competitive inhibition, which significantly influence exposure and impact efficacy and safety of substrate drugs. Consequently, both OATP1B-transporters became part of the preclinical assessment of new molecular entities during drug development in order to predict and avoid drug-drug interactions. After providing a brief overview on OATP-transporters, I willintroduce recent developments in the field where coproporphyrins are investigated as *in vivo* biomarkers of OATP1B-function. The coproporphyrins - coproporphyrin I and coproporphyrin III - are heme metabolites and the latter is also substrate of OATP2B1. This OATP shares multiple substrates with the well-studied OATP1B-transporters, but exhibits a much broader expression pattern with high abundance in ADME relevant organs. Even if identified two- decades ago, there is still only limited understanding on its clinical relevance. I will present ourexperimental approach to elaborate its *in vivo* function.

Short CV

Henriette E. Meyer zu Schwabedissen graduated 2004 from the School of Medicine of the Ernst-Moritz-Arndt University of Greifswald, and obtained her M.D. and license to practice in the same year. From 2004 to 2006 she was Resident at the Institute of Pharmacology at the University of Greifswald. In 2006, funded by the Deutsche Forschungsgemeinschaft, she joined the Group of Richard B. Kim in the Department of Clinical Pharmacology at the Vanderbilt University, Nashville, TN, USA. In the same year, she transferred to the University of Western Ontario, London, ON in Canada. 2008 she became Senior Scientist/Resident in the C_DAT Center of Drug Absorption and Transport (Department of Pharmacology) at the University of Greifswald. In March 2013, she was appointed Assistant Professor for Biopharmacy at the Department of Pharmaceutical Sciences at the University of Basel, and was promoted to Associate Professor in 2015.

Henriette Meyer zu Schwabedissen published over 100 research and review articles in peer reviewed journals, and is co-author of several book chapters and patent applications. Her research interests focus on mechanisms contributing to interindividual variability in drug response, with a major focus on drug transport.

Prof. Dr. Olivier Potterat

Division of Pharmaceutical Biology, University of Basel
e-Mail: olivier.potterat@unibas.ch

Library-based discovery of bioactive natural products

Abstract

The potential of natural products as a source of new lead compounds is undisputed. At the same time, the isolation of bioactive compounds from extracts by classical bioactivity-guided procedures is hardly compatible with the constraints of modern drug discovery. Profiling approaches have been therefore designed to identify more efficiently bioactive compounds in complex mixtures. In this context, we have set up a versatile strategy based on HPLC-based activity profiling in combination with an in-house extract library in 96-well plate format. This approach can be used with all miniaturized bioassays, and has been successfully applied in numerous screening projects performed in-house or in collaborative settings. Its potential will be illustrated by the discovery of potent activators of lymphangiogenesis from plants of the families Iridaceae and Thymelaeaceae, as well as structurally uncommon saponins modulating the expression and secretion of cytokines from saffron. The identification of promising development candidates in a project aimed at finding environmentally friendly alternatives to the use of copper in organic agriculture will be also presented.

Short CV

Olivier Potterat obtained a degree in Biology from the University of Lausanne (Switzerland) in 1985 and a PhD in Pharmacognosy/Phytochemistry with Prof. K. Hostettmann at the University of Lausanne in 1991. From 1991-1993, he was a Postdoctoral Fellow with Prof. H. Zähner (Microbiology) at the University of Tübingen (Germany). From 1993 to 1998, he was a Senior Researcher and then Assistant Professor at the Institute of Pharmacognosy, University of Lausanne. In 1998 he moved to the pharmaceutical company Böhringer-Ingelheim, where he was until 2005 in charge of the Natural Product Laboratory within the Lead Finding Department in Vienna (Austria) and later in Biberach/Riss (Germany). In April 2005, he joined the University of Basel (Switzerland) as a Senior Lecturer in the Division of Pharmaceutical Biology where he obtained his habilitation in 2009 and was appointed as a titular professor in 2018.

Olivier Potterat published over 90 research and review articles in peer reviewed journals, and is co-author of several book chapters and patent applications. From 2008 to 2015, he was Senior Editor of the international journal *Chemistry and Biodiversity*, and since 2016 he is an Editor of *Planta Medica*. In 2008 he received the *Sandoz Natura Phytotherapy Award*. His research interests focus on natural product based lead discovery and the investigation of active constituents in herbal medicines.

Yukihiro Furusawa

Toyama Prefectural University

Commensal microbiota maintains gut homeostasis through its metabolic products and epigenetic modification.

Abstract

Human bodies are composed of approximately 37 trillion cells, whereas the intestine alone harbors approximately 40 trillion bacteria. These bacteria form “commensal microbiota” that influence human health. Imbalance in commensal microbiota composition (termed “dysbiosis,” a state with abundant aggressive bacteria) causes immune disorders such as allergies and inflammatory bowel disease, the latter of whose incidence is increasing in developed countries. Recently, some kinds of microbiota have attracted considerable attention for their role in maintaining gut homeostasis by inducing differentiation of colonic regulatory T cells (Tregs), which suppress unfavorable immune responses not only to commensal microbiota but also allergic substances. However, the mechanism underlying Treg-induction by these microbes is still largely unknown. We previously revealed that short chain fatty acids (SCFAs), which are dietary fiber-derived metabolites produced by commensal bacteria, have the potential to induce colonic Treg cell differentiation through epigenetic modifications. Here, I present details of the mechanism underlying Treg cell induction by commensal microbe-derived SCFAs. In addition, I introduce an ongoing project aimed at inflammatory bowel disease prevention and treatment by application of dietary fibers that are a source of SCFAs and epigenetic drugs that promote Treg differentiation.

Short CV

- 2021-Present
  Associate Professor, Department of Pharmaceutical Engineering, Faculty of Engineering, Toyama Prefectural University

- 2020-2021
  Associate Professor, Department of Liberal Arts and Sciences, Toyama Prefectural University

- 2015-2020
  Lecturer, Department of Liberal Arts and Sciences, Toyama Prefectural University

- 2014-
  Assistant Professor, Division of Biochemistry, Faculty of Pharmacy, Keio University

- 2012-
  Assistant Professor (Project), The Institute of Medical Sciences, The University of Tokyo

- 2012-
  Postdoctoral Researcher, RIKEN Center for Integrative Medical Sciences

Dr. Yasuharu Watanabe

Toyama Prefectural Institute for Pharmaceutical Research

Crosstalk between neutrophils and adipocytes exacerbates adipose tissue inflammation in progression of type 2 diabetes

Obesity-associated adipose tissue inflammation contributes to the development of type 2 diabetes. Chronic activation of IL-1β system in adipose tissue on metabolic disorders is well demonstrated. However, a mechanism for its expression and activation in the tissue has remained unexplored.

We demonstrate that IL-1β transcript was enriched in neutrophils of visceral adipose tissue (VAT) from lean mice. Mechanistically, the interaction of neutrophils with adipocytes induced IL-1β expression via NF-κB pathway. Lipolysis of adipocytes accumulated neutrophils prior to macrophages in the VAT, and produced high levels of IL-1β via an inflammasome pathway. Leukotriene B_4 (LTB_4) production in the VAT also contributed to neutrophil accumulation. Furthermore, an LTB_4-inflammasome axis contributed to the expression of chemotactic molecules involved in high-fat diet–induced macrophageinfiltration into the VAT. We have identified previously unappreciated roles for neutrophils in the development of adipose tissue inflammation: robust IL-1β production and infiltration of macrophages to initiate chronic inflammation.

2003.4 ~ 2008.3	Graduate student, Graduate School of Life Sciences, Tohoku University, Japan
2008.4 ~ 2008.7	Postdoctoral fellow, Department of Biochemistry and Microbiology, Nelson Mandela Metropolitan University, South Africa
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